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STIC Database Tracking Number: 166911

TO: Christine Saoud
Location: REM-4E81/4C70
Art Unit: 1647
Tuesday, June 21, 2005

Case Serial Number: 09/801968

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Search Notes

RUSH

Please feel free to contact me if you have any questions or would like to amend the search.

Thank you for using STIC services.

Regards,
Deirdre Arnold

STIC-Biotech/ChemLib 156911

From: Chan, Christina
Sent: Monday, June 20, 2005 9:18 AM
To: Saoud, Christine; STIC-Biotech/ChemLib
Subject: RE: RUSH - 09/801,968

Please rush. Thanks Chris

Chris Chan
TC 1600 New Hire Training Coordinator and SPE 1644
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Remsen, 3E89

-----Original Message-----
From: Saoud, Christine
Sent: Friday, June 17, 2005 2:00 PM
To: Chan, Christina
Subject: RUSH - 09/801,968

Please search SEQ ID NO:4 in the pending and issued patent databases. This is a protein search. This is also an amended case, which is why we need the rush.

Thanks,
Christine Saoud
AU 1647
REM 04E81
571-272-0891

****
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Searcher:_____
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Type of Search

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Inventor:____ Litigation:___

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Vendors and cost where applicable
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US PATENT & TRADEMARK OFFICE

PATENT APPLICATION FULL TEXT AND IMAGE DATABASE

United States Patent Application *20020156001*
Kind Code **A1**
Econs, Michael ; et al. **October 24, 2002**

priority to 7/19/00

Novel fibroblast growth factor (FGF23) and methods for use

Abstract

The invention relates to novel nucleic acids encoding a fibroblast growth factor-23(FGF23) and proteins encoded thereby, mutations in which are associated with autosomal dominant rickets (ADHR). The invention further relates to methods of diagnosing and treating hypophosphatemic and hyperphosphatemic disorders comprising inhibiting or stimulating, respectively, the biological activity of FGF23 in a patient. The invention also relates to methods of treating osteoporosis, dermatomyositis, and coronary artery disease comprising stimulating the biological activity of FGF23 in a patient.

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Goverment Interests

[0002] The invention was made in part using funds obtained from the U.S. Government (National Institutes of Health Grant Nos. RO-1 AR42228, K24 AR02095, F32 AR08550) and the U.S. government may have certain rights in the invention.

Claims

What is claimed is:

1. An isolated nucleic acid encoding a fibroblast growth factor-23 (FGF23) or a mutant, variant, homolog, or fragment thereof.

2. An isolated nucleic acid encoding a fibroblast growth factor-23 (FGF23) wherein said isolated nucleic acid shares at least about 50% sequence identity with a nucleic acid sequence of at least one of SEQ ID NO:1 and SEQ ID NO:3.

3. An isolated nucleic acid encoding a fibroblast growth factor-23 (FGF23) wherein said isolated nucleic acid encodes a polypeptide having an amino acid sequence that shares at least 40% sequence identity with an amino acid sequence of at least one of SEQ ID NO:2 and SEQ ID NO:4.

4. An isolated nucleic acid included in DSMZ Deposit No. DSM 13530.

5. The isolated nucleic acid of claim 1, said isolated nucleic acid further comprising a nucleic acid encoding a tag polypeptide covalently linked thereto.

6. The isolated nucleic acid of claim 5, wherein said tag polypeptide is selected from the group consisting of a myc tag polypeptide, a glutathione-S-transferase tag polypeptide, a green fluorescent protein tag polypeptide, a myc-pyruvate kinase tag polypeptide, a His6 tag polypeptide, an influenza virus hemagglutinin tag polypeptide, a flag tag polypeptide, and a maltose binding protein tag polypeptide.

7. The isolated nucleic acid of claim 1, said nucleic acid further comprising a nucleic acid specifying a promoter/regulatory sequence operably linked thereto.

8. A vector comprising the isolated nucleic acid of claim 1.

9. The vector of claim 8, said vector further comprising a nucleic acid specifying a promoter/regulatory sequence operably linked thereto.

10. A recombinant cell comprising the isolated nucleic acid of claim 1.

11. A recombinant cell comprising the vector of claim 8.

12. An isolated nucleic acid complementary to a nucleic acid encoding a fibroblast growth factor-23 (FGF23) or a mutant, variant, homolog, or fragment thereof, said complementary nucleic acid being in an antisense orientation.

13. The isolated nucleic acid of claim 12, wherein said complementary nucleic acid shares at least 50% sequence identity with a nucleic acid complementary with a nucleic acid having the sequence of at least one of SEQ ID NO:1 and SEQ ID NO:3.

14. A vector comprising the isolated nucleic acid of claim 12.

15. The vector of claim 14, said vector further comprising a nucleic acid specifying a promoter/regulatory sequence operably linked thereto.

16. A recombinant cell comprising the isolated nucleic acid of claim 12.

17. A transgenic non-human mammal comprising an isolated nucleic acid encoding a fibroblast growth factor-23 (FGF23) or a mutant, variant, homolog, or fragment thereof.

18. An isolated polypeptide comprising a fibroblast growth factor-23 (FGF23) or a mutant, variant, homolog, or fragment thereof.

19. The isolated polypeptide of claim 18, wherein the amino acid sequence of said FGF23 shares at least about 40% sequence identity with an amino acid sequence of at least one of SEQ ID NO:2 and SEQ ID NO:4.

20. An antibody that specifically binds with a fibroblast growth factor-23 (FGF23) polypeptide, or a mutant, variant, homolog, or fragment thereof.

21. The antibody of claim 20, wherein said antibody is selected from the group consisting of a polyclonal antibody, a monoclonal antibody, a humanized antibody, a chimeric antibody, and a synthetic antibody.

22. An isolated nucleic acid encoding a fibroblast growth factor-23 (FGF23) wherein said nucleic acid comprises a mutation.

23. The isolated nucleic acid of claim 22, wherein said mutation confers increased stability on said FGF23.

24. The isolated nucleic acid of claim 22, wherein said mutation is selected from the group consisting of a mutation in the nucleic acid encoding amino acid 176 (arginine) relative to SEQ ID NO:2 and a mutation in the nucleic acid encoding amino acid 179 (arginine) relative to SEQ ID NO:2.

25. An isolated fibroblast growth factor-23 (FGF23) polypeptide, wherein said polypeptide comprises a mutation.

26. An isolated fibroblast growth factor-23 (FGF23) polypeptide, said polypeptide comprises a mutation that confers increased stability on said FGF23.

27. The isolated polypeptide of claim 26, wherein said mutation is selected from the group consisting of a mutation at amino acid 176 (arginine) relative to SEQ ID NO:2 and a mutation at amino acid 179 (arginine) relative to SEQ ID NO:2.

28. An inhibitor of fibroblast growth factor-23 (FGF23) wherein said inhibitor is selected from the group consisting of a molecule that reduces the level of mRNA encoding FGF23 polypeptide, a molecule that reduces the level of FGF23 polypeptide, and a molecule that reduces a biological activity of FGF23.

29. The inhibitor of claim 28, wherein said inhibitor is selected from the group consisting of an antisense nucleic acid, a ribozyme, an antibody, a peptide, and a peptidomimetic.

30. The inhibitor of claim 28, wherein said inhibitor is an antibody selected from the group consisting of an antibody that specifically binds with FGF23 and an antibody that specifically binds with an FGF23 receptor.

31. The inhibitor of claim 28, wherein said inhibitor is double stranded RNA that reduces the level of said mRNA encoding FGF23 polypeptide by RNA interference.

32. A composition comprising the isolated nucleic acid of claim 1 and a pharmaceutically-acceptable carrier.

33. A composition comprising the isolated nucleic acid of claim 12 and a pharmaceutically-acceptable carrier.

34. A composition comprising the isolated polypeptide of claim 18 and a pharmaceutically-acceptable carrier.

35. A composition comprising the antibody of claim 20 and a pharmaceutically-acceptable carrier.

36. A composition comprising the isolated nucleic acid of claim 22 and a pharmaceutically-acceptable carrier.

37. A composition comprising the isolated nucleic acid of claim 23 and a pharmaceutically-acceptable carrier.

38. A composition comprising the isolated nucleic acid of claim 24 and a pharmaceutically-acceptable carrier.

39. A composition comprising the isolated FGF23 polypeptide of claim 25 and a pharmaceutically-acceptable carrier.

40. A composition comprising the isolated FGF23 polypeptide of claim 26 and a pharmaceutically-acceptable carrier.

41. A composition comprising the isolated FGF23 polypeptide of claim 27 and a pharmaceutically-acceptable carrier.

42. A composition comprising the inhibitor of claim 28 and a pharmaceutically- acceptable carrier.

43. A method of making an isolated protein having the biological activity of fibroblast growth factor-23 (FGF23) comprising (a) culturing the recombinant cell of claim 11 under conditions such that said protein is expressed; and (b) recovering said protein.

44. A method of diagnosing a hypophosphatemic disorder in a mammal, said method comprising (a) obtaining a biological sample from said mammal and (b) contacting said biological sample with a reagent which detects the presence or absence of a mutation in a nucleic acid encoding fibroblast growth factor-23 (FGF23) wherein the presence of said mutation is an indication that said mammal is afflicted with said hypophosphatemic disorder, thereby diagnosing said hypophosphatemic disorder in said mammal.

45. The method of claim 44, wherein said hypophosphatemic disorder is autosomal dominant hypophosphatemic rickets (ADHR).

46. The method of claim 44, wherein said biological sample is selected from the group consisting of blood and urine.

47. The method of claim 44, wherein said reagent is a nucleic acid.

48. The method of claim 44, wherein said reagent is detectably labeled.

49. The method of claim 44, wherein said reagent is detectably labeled with a label selected from the group consisting of a radioisotope, a bioluminescent compound, a chemiluminescent compound, a fluorescent compound, a metal chelate, and an enzyme.

50. A method of diagnosing a hypophosphatemic disorder in a mammal, said method comprising (a) obtaining a biological sample from said mammal and (b) contacting said biological sample with a reagent which detects the presence or absence of a mutant form of fibroblast growth factor-23 (FGF23) polypeptide, wherein the presence of said mutant form of FGF23 polypeptide is an indication that said mammal is afflicted with said hypophosphatemic disorder, thereby diagnosing said hypophosphatemic disorder in said mammal.

51. The method of claim 50, wherein said hypophosphatemic disorder is autosomal dominant hypophosphatemic rickets (ADHR).

52. The method of claim 50, wherein said biological sample is selected from the group consisting of blood and urine.

53. The method of claim 50, wherein said reagent is an antibody.

54. A method of diagnosing a hypophosphatemic disorder in a mammal, said method comprising (a) obtaining a biological sample from said mammal and (b) contacting said biological sample with a reagent that detects the level of fibroblast growth factor-23 (FGF23) polypeptide in said sample, wherein an elevated level of FGF23 polypeptide in said sample, relative to the level of FGF23 polypeptide in a sample obtained from a control mammal, is an indication that said mammal is afflicted with said hypophosphatemic disorder, thereby diagnosing said hypophosphatemic disorder in said mammal.

55. The method of claim 54, wherein said hypophosphatemic disorder is selected from the group consisting of X-linked hereditary rickets (XLH), hereditary hypophosphatemic rickets (HHRH), hypophosphatemic bone disease (HBD), autosomal dominant hypophosphatemic rickets (ADHR), tumor induced osteomalacia, epidermal nevus syndrome, fibrous dysplasia, and nephrolithiasis.

56. The method of claim 54, wherein said biological sample is selected from the group consisting of blood and urine.

57. The method of claim 54, wherein said reagent is an FGF23 antibody.

58. The method of claim 54, wherein said reagent is detectably labeled.

59. The method of claim 54, wherein said reagent is detectably labeled with a label selected from the group consisting of a radioisotope, a bioluminescent compound, a chemiluminescent compound, a fluorescent compound, a metal chelate, and an enzyme.

60. A method of diagnosing tumor induced osteomalacia in a patient, said method comprising (a) obtaining a tumor sample from said patient and (b) detecting the expression or lack thereof of FGF23 in said tumor, wherein the expression of FGF23 is indicative that said patient has tumor induced osteomalacia.

61. A method of treating a hypophosphatemic disorder in a mammal, said method comprising administering to a mammal afflicted with said disorder a therapeutically effective amount of a fibroblast growth factor-23 (FGF23) inhibitor selected from the group consisting of an inhibitor which reduces the level of mRNA encoding FGF23 polypeptide in said mammal, an inhibitor which reduces the level of FGF23 polypeptide in said mammal, and an inhibitor of the biological activity of FGF23 in said mammal.

62. The method of claim 61, wherein said hypophosphatemic disorder is selected from the group consisting of X-linked hereditary rickets (XLH), hereditary hypophosphatemic rickets (HHRH), hypophosphatemic bone disease (HBD), autosomal dominant hypophosphatemic rickets (ADHR), tumor induced osteomalacia, epidermal nevus syndrome, fibrous dysplasia, and nephrolithiasis.

63. The method of claim 61, wherein said inhibitor is selected from the group consisting of an antisense nucleic acid, a ribozyme, an antibody, a peptide, and a peptidomimetic.

64. A method of treating a hyperphosphatemic disorder in a mammal, said method comprising administering to a mammal afflicted with said disorder a therapeutically effective amount of an isolated nucleic acid encoding fibroblast growth factor-23 (FGF23).

65. The method of claim 64, wherein said isolated nucleic acid comprises a mutation that confers increased stability on the FGF23 polypeptide encoded thereby.

66. The method of claim 64, wherein said hyperphosphatemic disorder is selected from the group consisting of mild renal insufficiency and tumoral calcinosis.

67. A method of treating a hyperphosphatemic disorder in a mammal, said method comprising administering to a mammal afflicted with said disorder a therapeutically effective amount of an isolated fibroblast growth factor-23 (FGF23) polypeptide.

68. The method of claim 67, wherein, said isolated FGF23 polypeptide comprises a mutation that confers increased stability on said FGF23 polypeptide.

69. The method of claim 67, wherein said hyperphosphatemic disorder is selected from the group consisting of mild renal insufficiency and tumoral calcinosis.

70. A method of treating a hyperphosphatemic disorder in a mammal, said method comprising administering to said mammal afflicted with said disorder a therapeutically effective amount of a reagent that increases the level of fibroblast growth factor-23 (FGF23) polypeptide is said mammal.

71. The method of claim 70, wherein said reagent inhibits degradation of said FGF23 polypeptide.

72. The method of claim 70, wherein said hyperphosphatemic disorder is selected from the group consisting of mild renal insufficiency and tumoral calcinosis.

73. A method of treating a hyperphosphatemic disorder in a mammal, said method comprising administering to a mammal afflicted with said disorder a therapeutically effective amount of a population of cells comprising an isolated nucleic acid encoding fibroblast growth factor-23 (FGF23).

74. The method of claim 73, wherein said isolated nucleic acid comprises a mutation that confers increased stability on said FGF23 encoded thereby.

75. The method of claim 73, wherein said hypophosphatemic disorder is selected from the group consisting of mild renal insufficiency and tumoral calcinosis.

76. A method of treating osteoporosis in a mammal, said method comprising administering to said mammal a therapeutically effective amount of a fibroblast growth factor-23 (FGF23) or a reagent that increases the level of FGF23 polypeptide in said mammal.

77. A method of treating a condition involving deposition of calcium and phosphate in the arteries or soft tissues of a mammal, said method comprising administering to said mammal a therapeutically effective amount of fibroblast growth factor-23 (FGF23) or a reagent that increases the level of FGF23 polypeptide.

78. The method of claim 77, wherein said condition is dermatomyositis.

79. A method of treating coronary artery disease in a mammal, said method comprising administering to the cells of the coronary artery of an afflicted mammal a nucleic acid encoding a fibroblast growth factor-23 (FGF23).

80. A kit for diagnosing a hypophosphatemic disorder in a mammal, said kit comprising a reagent which detects the presence or absence of a mutation in the nucleic acid sequence encoding fibroblast growth factor-23 (FGF23) wherein the presence of said mutation is an indication that said mammal is afflicted with said hypophosphatemic disorder, said kit further comprising an applicator, and an instructional material for the use thereof.

81. A kit for diagnosing a hypophosphatemic disorder in a mammal, said kit comprising a reagent that detects the level of a fibroblast growth factor (FGF23) polypeptide, wherein an elevated level of said FGF23 polypeptide is an indication that said mammal is afflicted with said hypophosphatemic disorder, said kit further comprising an applicator, and an instructional material for the use thereof.

82. A kit for diagnosing a hypophosphatemic disorder in a mammal, said kit comprising a reagent which detects the presence or absence of a mutant form of a fibroblast growth factor-23 (FGF23) polypeptide, wherein the presence of said mutant form of said FGF23 is an indication that said mammal is afflicted with said hypophosphatemic disorder, said kit further comprising an applicator, and an instructional material for the use thereof.

83. The isolated nucleic acid of claim 24, wherein said mutation is selected from the group consisting of 527G>A, 535C>T and 536G>A relative to SEQ ID NO:1.

Description

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority under 35 U.S.C. .sctn.119(e) to U.S. Provisional Application No. 60/219,137, filed on Jul. 19, 2000.

BACKGROUND OF THE INVENTION

[0003] Conditions in which serum phosphate levels are reduced or elevated, referred to as hypophosphatemia and hyperphosphatemia, respectively, are associated with a large and diverse group of clinically significant diseases. Hypophosphatemia, which often results from renal phosphate wasting, is caused by a number of genetic disorders including X-linked hypophosphatemic rickets (XLH), hereditary hypophosphatemic rickets with hypercalciuria (HHRH), hypophosphatemic bone disease (HBD), and autosomal dominant hypopohsphatemic rickets (ADHR). Hyperphosphatemia, observed in patients with mild renal insufficiency and tumoral calcinosis, can often be associated with soft tissue calcification, secondary hyperparathyroidism, tertiary hyperparathyroidism, and other metabolic derangements.

[0004] The molecular mechanisms by which proper serum phosphate concentrations are maintained are poorly understood. Identification of genes responsible for inherited disorders involving disturbances in phosphate homeostasis may provide insight into the pathways that regulate phosphate balance. Currently, despite clinical features apparent in patients with hypophosphatemic and hyperphosphatemic conditions, molecular markers useful in early diagnosis, grading, and staging of these disorders are not available. Likewise, the current lack of effective methods of treatment for patients with hypophosphatemic and hyperphosphatemic disorders presents a need for alternative therapies. The present invention fulfills these needs.

BRIEF SUMMARY OF THE INVENTION

[0005] The invention includes an isolated nucleic acid encoding FGF23 or a mutant, variant, homolog, or fragment thereof.

[0006] In one aspect, the isolated nucleic acid encoding FGF23 shares at least about 50% sequence identity with a nucleic acid sequence of at least one of SEQ ID NO:1 and SEQ ID NO:3.

[0007] The invention also includes an isolated nucleic acid encoding FGF23 wherein the isolated nucleic acid encodes a polypeptide having an amino acid sequence that shares at least 40% sequence identity with an amino acid sequence of at least one of SEQ ID NO:2 and SEQ ID NO:4.

[0008] In a preferred embodiment, the isolated nucleic acid of the invention is included in DSMZ Deposit No. DSM 13530.

[0009] In one aspect of the invention, the isolated nucleic acid encoding FGF23 is covalently linked to a nucleic acid encoding a tag polypeptide. In a preferred embodiment, the tag polypeptide is a myc tag polypeptide, a glutathione-S-transferase tag polypeptide, a green fluorescent protein tag polypeptide, a myc-pyruvate kinase tag polypeptide, a His6 tag polypeptide, an influenza virus hemagglutinin tag polypeptide, a flag tag polypeptide, or a maltose binding protein tag polypeptide.

[0010] The invention also includes a nucleic acid encoding FGF23, wherein the nucleic acid is operably linked to a nucleic acid specifying a promoter/regulatory sequence.

[0011] The invention further includes a vector comprising an isolated nucleic acid encoding FGF23. In a preferred embodiment, the vector comprises an isolated nucleic acid encoding FGF23 operably linked to a promoter/regulatory sequence.

[0012] The invention includes a recombinant cell comprising an isolated nucleic acid encoding FGF23 or a vector comprising the same.

[0013] The invention includes an isolated nucleic acid complementary to a nucleic acid encoding FGF23 or a mutant, variant, homolog, or fragment thereof, wherein the complementary nucleic acid is in an antisense orientation. In a preferred embodiment, the complementary nucleic acid shares at least 50% sequence identity with a nucleic acid complementary with a nucleic acid having the sequence of at least one of SEQ ID NO:1 and SEQ ID NO:3. Also included in the invention is a vector comprising the antisense nucleic acid, as well as a vector comprising the antisense nucleic acid operably linked to a nucleic acid specifying a promoter/regulatory sequence.

[0014] The invention further includes a recombinant cell comprising the antisense nucleic acid and vectors comprising the same.

[0015] The invention includes a transgenic non-human mammal comprising an isolated nucleic acid encoding FGF23 or a mutant, variant, homolog, or fragment thereof.

[0016] The invention further includes an isolated polypeptide comprising FGF23 or a mutant, variant, homolog, or fragment thereof. In a preferred embodiment, the isolated polypeptide shares at least about 40% sequence identity with an amino acid sequence of at least one of SEQ ID NO:2 and SEQ ID NO:4.

[0017] The invention includes an antibody that specifically binds with an FGF23 polypeptide, or a mutant, variant, homolog, or fragment thereof. In a preferred embodiment, the antibody is a polyclonal antibody, a monoclonal antibody, a humanized antibody, a chimeric antibody, or a synthetic antibody.

[0018] The invention further includes an isolated nucleic acid encoding FGF23, wherein the nucleic acid comprises a mutation. In a preferred embodiment, the mutation confers increased stability on FGF23. More preferably, the mutation affects amino acid 176 (arginine) relative to SEQ ID NO:2 or amino acid 179 (arginine) relative to SEQ ID NO:2. Even more preferably, the mutation is selected from the group consisting of 527G>A, 535C>T and 536G>A relative to SEQ ID NO:1.

[0019] The invention also includes an FGF23 polypeptide comprising a mutation. In a preferred embodiment, the FGF23 polypeptide comprises a mutation that confers increased stability. More preferably, the mutation is at amino acid 176 (arginine) relative to SEQ ID NO:2 or a mutation at amino acid 179 (arginine) relative to SEQ ID NO:2.

[0020] The invention includes an inhibitor of FGF23. The inhibitor can be a molecule that reduces the level of mRNA encoding FGF23 polypeptide, a molecule that reduces the level of FGF23 polypeptide, or a molecule that reduces a biological activity of FGF23. In a preferred embodiment, the inhibitor is an antisense nucleic acid, a ribozyme, an antibody, a peptide, or a peptidomimetic. More preferably, the inhibitor is an antibody that specifically binds with FGF23 or an antibody that specifically binds with an FGF23 receptor.

[0021] The invention includes a composition comprising an isolated nucleic encoding FGF23 and a

pharmaceutically-acceptable carrier.

[0022] The invention also includes a composition comprising an isolated nucleic acid complementary to a nucleic acid encoding FGF23 and a pharmaceutically-acceptable carrier.

[0023] The invention also includes a composition comprising an isolated FGF23 polypeptide and a pharmaceutically-acceptable carrier.

[0024] The invention also includes a composition comprising an antibody that specifically binds with FGF23 and a pharmaceutically-acceptable carrier.

[0025] The invention also includes a composition comprising an isolated nucleic acid encoding a mutant form of FGF23 and a pharmaceutically-acceptable carrier.

[0026] The invention also includes a composition comprising an isolated nucleic acid encoding a mutant form of FGF23 with increased stability and a pharmaceutically-acceptable carrier.

[0027] The invention also includes a composition comprising an isolated nucleic acid encoding a mutant form of FGF23 comprising a mutation at amino acid 176 (arginine) relative to SEQ ID NO:2 or a mutation at amino acid 179 (arginine) relative to SEQ ID NO:2 and a pharmaceutically-accept- able carrier.

[0028] The invention also includes a composition comprising an isolated FGF23 polypeptide comprising a mutation and a pharmaceutically-acceptable carrier.

[0029] The invention also includes a composition comprising an isolated FGF23 polypeptide comprising a mutation which confers increased stability and a pharmaceutically-acceptable carrier.

[0030] The invention also includes a composition comprising an isolated FGF23 polypeptide comprising a mutation at amino acid 176 (arginine) relative to SEQ ID NO:2 or a mutation at amino acid 179 (arginine) relative to SEQ ID NO:2 and a pharmaceutically-acceptable carrier.

[0031] The invention also includes a composition comprising an inhibitor of FGF23 and a pharmaceutically-acceptable carrier.

[0032] The invention further includes a method of diagnosing a hypophosphatemic disorder in a mammal. The method comprises (a) obtaining a biological sample from said mammal and (b) contacting said biological sample with a reagent which detects the presence or absence of a mutation in a nucleic acid encoding FGF23, wherein the presence of a mutation is an indication that the mammal is afflicted with the hypophosphatemic disorder, thereby diagnosing the hypophosphatemic disorder in the mammal.

[0033] In a preferred embodiment, the hypophosphatemic disorder is autosomal dominant hypophosphatemic rickets (ADHR).

[0034] In another preferred embodiment, the biological sample blood or urine.

[0035] In yet another preferred embodiment, the reagent is a nucleic acid. More preferably, the reagent is detectably labeled. Preferable labels include a radioisotope, a bioluminescent compound, a chemiluminescent compound, a fluorescent compound, a metal chelate, and an enzyme.

[0036] The invention includes a method of diagnosing a hypophosphatemic disorder in a mammal. The method comprises (a) obtaining a biological sample from said mammal and (b) contacting the biological sample with a reagent which detects the presence or absence of a mutant form of FGF23 polypeptide, wherein the presence of a mutant form of FGF23 polypeptide is an indication that the mammal is afflicted with the hypophosphatemic disorder, thereby diagnosing the hypophosphatemic disorder in the mammal.

[0037] In a preferred embodiment, the hypophosphatemic disorder is autosomal dominant hypophosphatemic rickets (ADHR).

[0038] In another preferred embodiment, the biological sample blood or urine.

[0039] In yet another preferred embodiment, the reagent is an antibody.

[0040] The invention includes a method of diagnosing a hypophosphatemic disorder in a mammal. The method comprises (a) obtaining a biological sample from said mammal and (b) contacting the biological sample with a reagent that detects the level of FGF23 polypeptide in the sample, wherein an elevated level of FGF23 polypeptide in the sample, relative to the level of FGF23 polypeptide in a control mammal, is an indication that the mammal is afflicted with the hypophosphatemic disorder, thereby diagnosing the hypophosphatemic disorder in the mammal.

[0041] In a preferred embodiment, the hypophosphatemic disorder is selected from the group consisting of X-linked hereditary rickets (XLH), hereditary hypophosphatemic rickets (HHRH), hypophosphatemic bone disease (HBD), autosomal dominant hypophosphatemic rickets (ADHR), tumor induced osteomalacia, epidermal nevus syndrome, fibrous dysplasia, or nephrolithiasis.

[0042] In another preferred embodiment, the biological sample is blood or urine.

[0043] In yet another preferred embodiment, the reagent is an FGF23 antibody. More preferably, the reagent is detectably labeled. Preferable labels include a radioisotope, a bioluminescent compound, a chemiluminescent compound, a fluorescent compound, a metal chelate, and an enzyme.

[0044] The invention further includes a method of diagnosing tumor induced osteomalacia in a patient. The method comprises (a) obtaining a tumor sample from the patient and (b) detecting the expression or lack thereof of FGF23 in the tumor, wherein the expression of FGF23 is indicative that the patient has tumor induced osteomalacia.

[0045] The invention also includes a method of treating a hypophosphatemic disorder in a mammal. The method comprises administering to a mammal afflicted with the disorder a therapeutically effective amount of an FGF23 inhibitor. The inhibitor can be an inhibitor which reduces the level of mRNA encoding FGF23 polypeptide in said mammal, an inhibitor which reduces the level of FGF23 polypeptide in said mammal, or an inhibitor of the biological activity of FGF23 in said mammal.

[0046] In a preferred embodiment, the hypophosphatemic disorder X-linked hereditary rickets (XLH), hereditary hypophosphatemic rickets (HHRH), hypophosphatemic bone disease (HBD), autosomal dominant hypophosphatemic rickets (ADHR), tumor induced osteomalacia, epidermal nevus syndrome, fibrous dysplasia, or nephrolithiasis.

[0047] In another preferred embodiment, the inhibitor is an antisense nucleic acid, a ribozyme, an antibody, a peptide, or a peptidomimetic.

[0048] The invention further includes a method of treating a hyperphosphatemic disorder in a mammal. The method comprises administering to a mammal afflicted with the disorder a therapeutically effective amount of an isolated nucleic acid encoding FGF23.

[0049] In a preferred embodiment, the isolated nucleic acid comprises a mutation that confers increased stability on the FGF23 polypeptide encoded thereby.

[0050] In another preferred embodiment, the hyperphosphatemic disorder mild renal insufficiency or tumoral calcinosis.

[0051] The invention also includes a method of treating a hyperphosphatemic disorder in a mammal. The method comprises administering to a mammal afflicted with the disorder a therapeutically effective amount of an isolated FGF23 polypeptide.

[0052] In a preferred embodiment, the isolated FGF23 polypeptide comprises a mutation that confers increased stability.

[0053] In another preferred embodiment, the hyperphosphatemic disorder mild renal insufficiency or tumoral calcinosis.

[0054] The invention further includes a method of treating a hyperphosphatemic disorder in a mammal. The method comprises administering to the mammal afflicted with the disorder a therapeutically effective amount of a reagent that increases the level of FGF23 polypeptide is the mammal.

[0055] In a preferred embodiment, the reagent inhibits degradation of FGF23 polypeptide.

[0056] In another preferred embodiment, the hyperphosphatemic disorder mild renal insufficiency or tumoral calcinosis.

[0057] The invention further includes a method of treating a hyperphosphatemic disorder in a mammal. The method comprises administering to a mammal afflicted the disorder a therapeutically effective amount of a population of cells comprising an isolated nucleic acid encoding FGF23.

[0058] In a preferred embodiment, the isolated nucleic acid comprises a mutation that confers increased stability on the FGF23 encoded thereby.

[0059] In another preferred embodiment, the hypophosphatemic disorder mild renal insufficiency or tumoral calcinosis.

[0060] The invention includes a method of treating osteoporosis in a mammal. The method comprises administering to the mammal a therapeutically effective amount of a FGF23 or a reagent that increases the level of FGF23 polypeptide in the mammal.

[0061] The invention further includes a method of treating a condition involving deposition of calcium and phosphate in the arteries or soft tissues of a mammal. The method comprises administering to the mammal a therapeutically effective amount of FGF23 or a reagent that increases the level of FGF23 polypeptide.

[0062] In a preferred embodiment, the condition is dermatomyositis.

[0063] The invention further includes a method of treating coronary artery disease in a mammal. The

method comprises administering to the cells of the coronary artery of an afflicted mammal a nucleic acid encoding a FGF23.

[0064] The invention also includes a kit for diagnosing a hypophosphatemic disorder in a mammal. The kit comprises a reagent which detects the presence or absence of a mutation in the nucleic acid sequence encoding FGF23 wherein the presence of the mutation is an indication that the mammal is afflicted with the hypophosphatemic disorder. The kit further comprises an applicator and an instructional material for the use thereof.

[0065] The invention also includes a kit for diagnosing a hypophosphatemic disorder in a mammal. The kit comprises a reagent that detects the level of FGF23 polypeptide, wherein an elevated level of FGF23 polypeptide is an indication that the mammal is afflicted with the hypophosphatemic disorder. The kit further comprises an applicator and an instructional material for the use thereof.

[0066] The invention also includes a kit for diagnosing a hypophosphatemic disorder in a mammal. The kit comprises a reagent which detects the presence or absence of a mutant form of a FGF23 polypeptide, wherein the presence of the mutant form of FGF23 is an indication that the mammal is afflicted with the hypophosphatemic disorder. The kit further comprises an applicator and an instructional material for the use thereof.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

[0067] The foregoing summary, as well as the following detailed description of preferred embodiments of the invention, will be better understood when read in conjunction with the appended drawings. For the purpose of illustrating the invention, there is shown in the drawings embodiments which are presently preferred. It should be understood, however, that the invention is not limited to the precise arrangements and instrumentalities shown.

[0068] In the drawings:

[0069] FIG. 1A is a diagram depicting linkage analysis within the pedigrees of two different ADHR families (1406 and 1478).

[0070] FIG. 1B is a series of diagrams of pedigrees and images of agarose gels depicting mutation analysis in three different ADHR families (1406, 1478, and 2318).

[0071] FIG. 2 is a diagram depicting a physical map of the ADHR region. The position of DNA markers and BACs/PACs are drawn to scale as estimated by the unfinished sequence data (Baylor College of Medicine Human Genome Sequencing Center). Arrows indicate gaps in the genomic sequence between clone RP11-303E5 and RP1 1-320N7, and clone RP11-103A11 and RP11-935C2. The approximate positions of genes between D12S1624 and D12S1594 and of GPR46 and GDF2 are indicated.

[0072] FIGS. 3A through 3C are an amino acid sequence alignment of FGF23 and other mammalian FGF family members (SEQ ID NOS:14-34 in the order in which they appear in the figure). The alignment is confined to the core sequence which consists of twelve antiparallel beta strands. The locations of the segments with beta-sheet conformation in the FGF-2 crystal structure are underlined. The two arginines which are mutated in FGF23 (FIG. 3C; indicated by asterisks) are conserved within the mouse homolog of FGF23. The alignment was generated with CLUSTAL and PRETTYBOX. Human and mouse FGF23 were identified by the FGF profile of the PFAM database (4.6e-14, 1.9e-16). They share 25% to 36% amino acid identity with the other members of the FGF family in the common core sequence.